Mechanical and Non-mechanical Factors in Hypertensive Hypertrophy, Their Clinical Roles

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To investigate the clinical roles of mechanical and non-mechanical factors in hypertensive hypertrophy, 125 patients with essential hypertension, 20 with hypertrophic cardiomyopathy (HCM) and 20 with dilated cardiomyopathy (DCM), were studied using echocardiography. The hypertensive patients were separated into 3 groups: those with left ventricular (LV) hypertrophy (H), those without hypertrophy (H(-)) and those with dilatation (D). Group H patients were separated into 3 subgroups: those with subnormal LV end-systolic wall stress (ESS) (HI), those with normal ESS and mild hypertrophy (HIIA), and those with normal ESS and severe hypertrophy (HIIB). The inotropic response to isoproterenol infusion ($0.02 \mu\text{g/kg/min}$ for 5 min) was measured by the increase of fractional shortening (FS) corrected for the decrease of ESS ($\Delta\text{FS}/\Delta\text{ESS}$). After antihypertensive treatment for 4.4 ± 1.7 years, echocardiography was repeated. $\Delta\text{FS}/\Delta\text{ESS}$ was significantly larger in HI and HCM than in HIIA, was significantly larger in HIIA than in HIIB in which it was significantly larger than in D and DCM. After the treatment, LV mass decreased significantly except in HI. In conclusion, hypertensive hearts are regulated by mechanical and non-mechanical factors. Non-mechanical factors, for example the function of beta-adrenergic receptors in myocardium, have a variety of influences on myocardium, causing a broad spectrum of clinical features and courses.

CHRONIC pressure overloading (mechanical factor) of the heart is believed to lead to wall thickening that is commensurate with an increased systolic pressure and tends to normalize myocardial wall stress (appropriate hypertrophy).^{1,2} In hypertrophic cardiomyopathy (HCM), the etiology of which is unknown, there is inappropriate hypertrophy,³ which must be

caused by factors other than mechanical overload (non-mechanical factors). Experimented evidence suggests that, as well as a mechanical factor, neurohormonal influences could have an important role in a left ventricular hypertrophy (LVH) in hypertension.⁴

We have attempted to classify clinical hypertensive LVH on the basis of its mechanical and non-mechanical factors, and to investigate their roles in clinical pictures and courses.

Key words:

Hypertensive hypertrophy
Mechanical factor
Non-mechanical factor
Beta-adrenergic receptor
Regression of hypertrophy

PATIENTS AND METHODS

Patients: We studied 125 patients who had

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Fig.1. Relation between left ventricular end-systolic wall stress (ESS) and fractional shortening (FS) before the infusion of isoproterenol in all the hypertensive patients. The broken lines show the regression line and 95% confidence interval.

had hypertension for more than 5 years. The blood pressure (BP) was measured by a cuff sphygmomanometer, using phases 1 and 5 of the Korotkoff sounds. Arterial hypertension was defined as a persistent systolic BP greater than 150 mmHg or a diastolic BP greater than 95 mmHg before any antihypertensive treatment was initiated or 4 weeks after the discontinuation of antihypertensive drugs.

The patients were separated into 3 groups: 1) patients with LVH (H, 70 cases), 2) patients without LVH (H(-), 36 cases) and 3) patients with left ventricular (LV) dilatation (D, 19 cases). Echocardiographic evidence of LVH was: (a) interventricular septal wall thickness (IVST) of ≥ 12 mm at the end-diastole, (b) LV end-diastolic posterior wall thickness (PWT) of ≥ 12 mm, and (c) LV mass greater than 2 standard deviations (SD) above the normal mean. Those who had a left ventricular end-diastolic diameter (LVEDd) of 55 mm or more were classified into Group D, even if they had LVH. None of these patients had evidence of any other heart disease from their cardiovascular history, physical examination, ECG, or echocardiography; and they had a sinus rhythm without signs of heart failure. Because coronary arteriography was not justified in these patients, concomitant coronary

artery disease had to be excluded on clinical grounds alone. Thus the patients in this study had arterial hypertension without any clinically evident coronary artery disease.

Twenty patients with HCM and twenty patients with dilated cardiomyopathy (DCM) were also studied. The diagnoses of HCM or DCM were made by ventriculography and/or ultrasonic echocardiography.

All the patients consented to the following tests.

Estimation of LV structure and function: M mode and cross sectional echocardiograms were obtained with a Toshiba SSH-11A cross sectional ultrasonoscope with a 2.25 MHz transducer. A cross sectional echocardiogram was recorded on a video system (Victor Umatic CR 6060) and M mode echocardiograms were photographed on light sensitive paper (Kodak Linagraph, 1985) at a paper of 50 mm/s using a Honeywell 1956 strip chart recorder. The echocardiograms were obtained during expiration. The measurements were taken by 2 observers (who were unaware of the patient's clinical state) from at least 6 consecutive cardiac cycles, using standard conventions.

Fractional shortening (FS, %) (an index of the ejection phase) was calculated as $(LVEDd -$

Fig.2. The changes of relation between left ventricular end-systolic wall stress (ESS) and fractional shortening (FS) after isoproterenol in Groups HI, HIIA and HIIIB. The arrows show the changes in individual patients. The broken lines show the regression line with 95% confidence interval. (from Sugishita et al¹¹ with permission)

$\text{LVESd}/\text{LVEDd} \times 100$, where LVESd was LV end-systolic diameter. LV mass (g) was calculated by a pathologically validated regression method: $1.05 [(\text{LVEDd} + \text{IVST} + \text{PWT})^3 - \text{LVEDd}^3] - 145$. The end-systolic wall stress (ESS, g/cm^2) was calculated by the equation: $1.36 \times (\text{peak arterial pressure}) \times (\text{LVESd}^2)/4$ (LV end-systolic wall thickness) $\times (\text{LVESd} + \text{LV end-systolic wall thickness})^6$ (Systolic BP was used for the peak arterial pressure.) This is an expression of the

average meridional wall stress which may be defined as the force per unit area acting at the equatorial plane of the ventricle in the direction of the apex-to-base axis. The calculation of the ESS from these measures has been validated^{7,8}

Group H patients were separated into 2 subgroups: Group HI consisted of 21 patients with $\text{ESS} < 2\text{SD}$ below the normal mean ($< 36.4 \text{ g}/\text{cm}^2$) and Group HII consisted of 49 patients with ESS within 2SD of the normal mean. (No patient in this study had ESS more than 2SD above the normal mean.) It has been reported that the mean LV mass calculated echocardiographically in hypertensive patients with LVH is approximately twice the normal mean value^{9,10}. So we divided Group HII into 2 subgroups: Group HIIA consisted of 37 patients with LV mass of twice the normal mean or less ($\leq 360\text{g}$) and Group HIIIB consisted of 12 patients with LV mass more than twice the normal mean ($> 360\text{g}$).

Adrenergic responses (Isoproterenol (ISP) echocardiography): The study was performed in the afternoon in all the subjects. Simultaneous cross sectional and M mode echocardiographic and ECG baseline recordings and BP measurements were performed with the patient in a supine position immediately before intravenous infusion of ISP ($0.02 \mu\text{g}/\text{kg}/\text{min}$) via a calibrated infusion pump. After 5 min of infusion, cross sectional and M mode echocardiograms and an ECG were recorded and BP was measured by cuff sphygmomanometer¹¹. The transducer was held on the same part of the chest wall throughout the examinations. To standardize the technique between patients, as well as in the same patient before and after the infusion of ISP, we tried to record the echocardiograms at the same part of the left ventricle (just below the tip of the anterior mitral leaflet) before and after the infusion of ISP. The beams of M mode echocardiography were aligned perpendicularly with the posterior walls of the left ventricle and with the wall of the interventricular septum in all the patients both before and after the infusion of ISP. Wall motion abnormality was shown the infusion of ISP in none of the patients.

Follow up: After a baseline echocardiographic study was obtained (with ISP study), antihypertensive treatment was initiated in the hypertensive patients. The antihypertensive drugs used were not standard, since they were determined by the individual doctors in the outpatient clinic. After a follow-up period of

Fig.3. The increase of fractional shortening produced by infusion of isoproterenol (Δ FS) after correction for the decrease of left ventricular end-systolic wall stress (Δ ESS) (Δ FS/ Δ ESS), in Groups HCM, HI, HIIA and HIIB (modified from Sugishita et al,¹¹ with permission).

4.4 ± 1.7 years, the echocardiographic studies were repeated. In Group H, the studies were repeated in only 15 patients in Group HI and 21 patients in Group HII, who were systolic BP-matched.¹² There were no significant differences in the follow-up period and administered drugs among the groups.

Statistical analysis: We used the t test, paired t test, correlation, regression equations and F test. All results in which $p < 0.05$ were regarded as statistically significant.

RESULTS

Hemodynamic and echocardiographic findings at baseline: There were no significant differences in age, sex and heart rate among the groups. Among the hypertensive patients, systolic BP was significantly lower in Group HI than in the others (vs. HIIA: $p < 0.01$; vs. D: $p < 0.02$), but diastolic BP was not significantly different among them.

Figure 1 shows the relation between FS and ESS before the infusion of ISP in all the hyper-

Fig.4. The changes of the left ventricular mass with antihypertensive treatment in Groups HI, HII, H(-) and D. The left half was reprinted with permission from the American College of Cardiology (JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, 1990; 15: 665-71).

tensive patients, suggesting a similar level of myocardial contractility among the groups. There was a statistically significant inverse linear relation between FS and ESS ($r = 0.89$, $p < 0.001$).

Adrenergic responses: Fig. 2 shows the changes in the relation between FS and ESS in Groups H.¹¹ It suggests that there was a different slope for each of the groups. Fig. 3 shows the increase of FS corrected for the decrease of ESS, that is the slope of the change of the relation between FS and ESS (HCM, Groups HI, HIIA and HIIB¹¹). This variable (Δ FS/ $-\Delta$ ESS) shows the response of myocardial contractility to ISP because the changes in this variable are within the range in which FS and ESS are linearly related in Fig. 1. This variable was significantly larger in HCM and Group I than in Group HIIA ($p < 0.05$), and was significantly larger in Group HIIA than in Group HIIB ($p < 0.05$).¹¹ It was

Fig.5. Schematic diagram of the possible roles of mechanical and non-mechanical factors in the etiology of hypertensive hearts, in comparison with hypertrophic cardiomyopathy and dilated cardiomyopathy. (NS: nervous system)

similar in Groups HIIB and H(-), was significantly smaller in Group D than in Group H(-), and was similar in group D and DCM.

Follow up: The systolic BP decreased significantly in the hypertensive groups ($p < 0.001$), and there was no significant difference in the change of the systolic BP between the groups.¹² LVEDd decreased significantly in Group D. FS did not change significantly. IVST and PWT did not change in Group HI, although both decreased to a level statistically significant in Group HII.¹² (These changes were close to the limits of variability due to measurement error).¹³

The changes in the LV mass are shown in Fig. 4 (Groups HI and HII were systolic BP matched).¹² In Group HI, the mass increased significantly ($p < 0.05$), although some patients in the group experienced no change. On the contrary, in Groups H(-) and D, the LV mass decreased significantly ($p < 0.001$). The changes in the LV mass were not equal in all individuals in either group. One of the reasons may be that various kinds of antihypertensive drugs, each having different abilities to induce regression of LVH, such as calcium antagonists, beta-blocker and diuretics, were used in the patients in this study.

DISCUSSION

LV ejection phase indices and wall stress: An

inverse linear correlation was found between FS and ejection fraction and LV wall stress in normal controls,^{14,15} in hypertension,¹⁶ and in other heart diseases.^{17,18} An inverse curvilinear correlation has also been reported between the velocity of LV fiber shortening and LV wall stress.¹⁷ In our study we used $\Delta FS/\Delta ESS$ as an index of the response of myocardial contractility in the range in which FS and ESS were considered to be related linearly in Fig. 1.

Adrenergic response in hypertensive LVH: It has been suggested that, as well as mechanical factors, neurohormonal influences could have an important role in the LVH of hypertension.⁴ Small doses of catecholamines produced LVH in laboratory animals without changing BP and heart rate.^{19,20}

The etiology of HCM is not yet known. A disorder of catecholamine function has been suggested,²¹ and hypersensitivity of the beta adrenergic receptor system has been proposed to explain HCM with asymmetric septal hypertrophy.²²

In patients in Group HI, ESS was less than normal, and these patients were more responsive to ISP than those with the other types of hypertensive LVH, as those with HCM. LVH in Group HI may be the result of a combination of the hypertension and factor causing HCM; this second factor will be difficult to identify since in HCM, by definition, there is no cause estab-

lished. Alternatively, patients in Group HI may have had an early stage of hypertension; this is not likely, however, as these patients were not young and they had had hypertension for at least 5 years.

Group HIIB (severe LVH) was significantly less responsive to ISP than Group HIIA (mild LVH) ($p < 0.01$). This clinical result may support the experimental results of others.^{2,3} The blunting of inotropic responsiveness to beta-adrenergic stimulation may be one of the mechanisms causing progression from LVH to heart failure in hypertensive disease.

Adrenergic response in hypertension without LVH or with dilatation: The prevalence of LVH was 23 to 48% in hypertensive patients and 0 to 10% in normal subjects.²⁴⁻²⁶ These data establish that LVH does not occur in all patients with mild to moderately severe essential hypertension. It has been suggested that the function of beta-adrenergic receptors is depressed in Group H(-).

In Group D, $\Delta\text{FS}/-\Delta\text{ESS}$ was significantly smaller than in hypertensive patients without LVH, as similar to in DCM. This suggests that, in the patients with LV dilatation, the function of beta-adrenergic receptors in myocardium may be depressed.

Follow up: It is known that the regression of LVH in hypertension is dependent on the anti-hypertensive drug administered. It might be also dependent on the state of the heart.

In hypertensive patients with normal ESS, LVH (appropriate hypertrophy) might have been induced by a mechanical factor (high BP), and the LVH might have regressed by unloading the mechanical load with an antihypertensive drug, if the drug had a potency to regress LVH. On the other hand, in those with subnormal ESS, LVH (inappropriate hypertrophy) might have been induced by a non-mechanical (probably neurohormonal) factor, and the LVH could not regress by a decrease of BP caused by antihypertensive drug, even if the drug had a potency to regress LVH.¹²

It has been reported that the progress of LVH is present in some adult patient with HCM.²⁷

Mechanisms of hypertrophy or dilation in left ventricle in hypertension: Chronic pressure overloading in hypertension is a mechanical factor. Even if the mechanical factor were at the same level, LV changes in hypertension might be variable, probably due to the variable influences of non-mechanical factors. As shown in Fig. 5, non-mechanical factors have a variety

of effects, from increasing LVH to inhibition of LVH (= dilatation), causing a broad spectrum of clinical features in hypertensive hearts. When there is no non-mechanical factor, as shown in the center of Fig. 5, mechanical factor induces appropriate hypertrophy (Group HIIA), which progresses to severe hypertrophy (Group HII) and to heart failure. When there is a non-mechanical factor, which increases LVH, inappropriate hypertrophy is induced, as in Group HI, which has clinical features similar to HCM. When there is a non-mechanical factor, which inhibits LVH or increases dilatation, it does not cause LVH but dilatation, which is similar to DCM.

Non-mechanical factors remain to be investigated, but beta-adrenergic receptors in myocardium may be important. We found that beta-adrenergic response was accelerated in the progenies of hypertensive patients with LVH to greater extent than in those of the hypertensive patients without LVH (unpublished data). This suggests that the non-mechanical factor might be regulated by a predisposition in the adrenergic receptors of the myocardium.

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